

ability to ketoacidosis and their more general perceptions of control of diabetes provided useful pointers to risks of subsequent ketoacidosis during use of continuous subcutaneous infusion.

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## Spontaneous pneumomediastinum in two stowaways

We describe two cases of pneumomediastinum which occurred in stowaways on a banana boat arriving at Avonmouth Docks, Bristol, from Columbia, South America. The voyage took 17 days, during which time the two men ate and drank very little. The temperature in the hold of the ship was 54-59°C.

### Case reports

**Case 1**—A 23 year old man was hypothermic (34.8°C), moderately dehydrated, and, except for resting tachycardia of 96 beats/min, showed no abnormal cardiovascular or respiratory signs. There was evidence of cold injury to both feet. Investigations showed blood urea concentrations of 76 mmol/l (458 mg/100 ml), creatinine 475 µmol/l (5.4 mg/100 ml), sodium 155 mmol(mEq)/l, chloride 105 mmol(mEq)/l, bicarbonate 21 mmol(mEq)/l, and potassium 4.4 mmol(mEq)/l. Concentration of urinary sodium was 28 mmol/l and urea 401 mmol/l (2.4 g/100 ml), indicating dehydration with prerenal uraemia and no metabolic acidosis. Biochemical values returned to normal when the patient was rehydrated. The patient complained of chest pain, worsened by breathing and recumbency. Despite the absence of physical signs in the chest a radiograph showed mediastinal and soft tissue emphysema. This resolved within five days. He was found to be infested with *Ascaris lumbricoides*.

**Case 2**—A 19 year old man was also hypothermic (35.2°C) and moderately dehydrated with a resting tachycardia of 100 beats/min. There were no other abnormal physical signs. The blood urea concentration was 44.5 mmol/l (268 mg/100 ml), creatinine 171 µmol/l (1.9 mg/100 ml), sodium 152 mmol/l, chloride 105 mmol/l, bicarbonate 25 mmol/l, and potassium 3.7 mmol/l. Urinary sodium concentration was 7 mmol/l and urea 696 mmol/l (4.2 g/100 ml), which again confirmed dehydration with prerenal uraemia but no metabolic acidosis. These measures became normal when the patient was rehydrated. Routine chest radiography showed emphysema of the mediastinum and chest wall. There were no symptoms or signs, however, of either of these conditions. Resolution occurred within five days. He was infested with *Trichuris trichiura*, *Necator americanus*, and *Strongyloides stercoralis*.

### Comment

Air reaching the mediastinum from the interstitial tissues of the lungs results from rupture of marginal alveolar bases and may occur when there is a sudden rise of intra-alveolar pressure. The pathophysiological mechanism that results in interstitial air in cases of asthma has been elucidated by Macklin and Macklin.<sup>1</sup> They found that bronchospasm, mucosal oedema, and inspissation of secretions in people with asthma caused air to be trapped with resulting stretching of alveoli. Supporting structures such as the pulmonary arteries, veins, and alveolar septa have limited elasticity, and as distension increases shearing forces, developed by exaggerated respiratory effort, rupture the marginal alveolar bases. The escaping air dissects along the perivascular sheaths towards the hilum.

Similar mechanisms have been postulated in pneumomediastinum associ-

ated with artificial ventilation, parturition, strenuous exercise, and diabetic ketosis. In diabetic ketosis the rise in intra-alveolar pressure is thought to be a result of repeated vomiting. This is also thought to cause some cases of pneumomediastinum in patients with anorexia nervosa. Pneumomediastinum, however, has been reported in the absence of vomiting in a girl with anorexia nervosa and in an emaciated adolescent boy with functional anorexia of a month's duration.<sup>2,3</sup> Experimental work on rats' lungs has shown that an inadequate diet, by decreasing tissue elasticity and increasing surface forces, may result in air trapping owing to premature closure of the airway.<sup>4</sup> Microscopic examination of these lungs showed a decrease in the volume density of lamellar bodies, mitochondria, and cytoplasm. As the granular pneumocyte lamellar bodies are the site of surfactant storage, its reduction may partly account for the altered mechanics, and hence a cellular cause for the raised intra-alveolar pressure is possible.

The possibility that similar changes might occur during starvation and account for pneumomediastinum in patients with anorexia nervosa where vomiting is not a factor has previously been considered.<sup>3,4</sup> These stowaways had been in the ship's hold for nearly three weeks with very little food or water. Their diet before this was possibly poor, and, moreover, both were infested with intestinal worms. The mechanism of pneumomediastinum in their cases might be similar to that postulated in some patients with anorexia nervosa.

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## Life threatening reaction to tuberculin testing

Severe anaphylactoid reactions after tuberculin testing are rarely seen nowadays. We report on a patient who developed an acute severe systemic upset with renal failure and hepatic dysfunction after an intradermal injection of 0.1 ml tuberculin purified protein derivative at a 1:10 000 dilution (1 IU).

### Case report

A 35 year old Portuguese woman, who had lived in England for 14 years, presented with a two month history of cervical lymphadenopathy. She was otherwise well. Histological examination of a lymph node biopsy specimen had shown epithelioid granulomata but no acid fast bacilli on Ziehl-Neelsen staining; the tissue was set up for culture. All initial investigations, including renal and hepatic function, were normal. A 0.1 ml sample of a 1:10 000 (1 IU) diluted tuberculin purified protein derivative was given intradermally in the right forearm. Within three hours of this injection she developed a fever with rigors, sweating, and profuse vomiting; over the next 48 hours her condition deteriorated with generalised aches and pains, dry cough, and oliguria. On admission to hospital she was feverish (39°C) with a low volume tachycardia (120 beats/minute) and a blood pressure of 70/40 mm Hg. There was no reaction at the site of the tuberculin injection.

Investigations showed a white cell count of  $9 \times 10^9/l$  with normal differential; concentrations of urea 24.3 mmol/l (normal range 3.0-6.5 mmol/l) (146 mg/100 ml (18-39 mg/100 ml)), sodium 130 mmol (mEq)/l (135-145 mmol (mEq)/l), potassium 3.4 mmol (mEq)/l (3.5-5.0 mmol (mEq)/l), and total bilirubin 45 µmol/l (5-17 µmol/l) (2.7 mg/100 ml (0.3-1.0 mg/100 ml)); activities of aspartate transaminase 117 IU/l (5-40 IU/l) and alkaline phosphatase 207 IU/l (35-130 IU/l); concentration of total protein 64 g/l (60-80 g/l) with an albumin concentration of 36 g/l (30-50 g/l); prothrombin time 17 seconds (11-14 seconds) and partial thromboplastin time 43 seconds (30-40 seconds) but no fibrinogen degradation products. The patient's urinary volume was less than 2 ml/hour; a 24 hour urinary collection showed a total protein concentration of 1.20 g/l (0.05), sodium concentration 62 mmol/l (100-250 mmol/l), potassium concentration 45 mmol/l (40-120 mmol/l) and urea concentration 183 mmol/l (170-600 mmol/l) (1.1 (1.0-3.6

mg/100 ml)). Blood urine, stool, and sputum cultures; throat and vaginal swabs; and a viral screen all yielded negative results. The chest radiograph, electrocardiogram, and renal ultrasound scan were normal. A plain abdominal radiograph showed an intrauterine device. She was resuscitated with intravenous fluids and hydrocortisone infusion (200 mg/eight hours for 36 hours). Cefotaxime and metronidazole were given but withdrawn when all cultures were reported to have yielded negative results. The patient improved clinically within 24 hours, her renal and hepatic function returning to normal over the subsequent weeks.

On the fourth day after the Mantoux test an intense erythematous induration (5×6 cm) was noted at the site of injection and this persisted for eight weeks. The culture of the lymph node biopsy specimen grew a fully sensitive *Mycobacterium tuberculosis*. The patient was given rifampicin and isoniazid, initially at a dose of 150 mg and 100 mg daily, respectively, to prevent rifampicin induced toxic shock,<sup>1</sup> which was titrated to a maintenance dose of 600 mg and 300 mg daily, respectively, over a week. She was discharged receiving this regimen and remained clinically well.

## Comment

There have been previous reports of transient fever, shivering, vomiting, and arthralgia after tuberculin testing.<sup>2</sup> Severe anaphylactoid reactions, however, as seen in our patient, are rarely reported. In the past they were observed when preparations of tuberculin were used to desensitise patients with known tuberculosis. The so called "paraphylactoid shock" or "systemic tuberculin shock"<sup>3,4</sup> occurred within 24 hours of the injection and included rigors, nausea and vomiting, arthralgia, headaches, jaundice, adrenal insufficiency, wheezing, and renal failure with proteinuria and oliguria. The reactions either subsided within 48 hours or progressed with further clinical deterioration. Such adverse effects were noted despite the use of a highly purified form of tuberculin.

In our case we had used a dilute solution of 1:10 000 tuberculin (1 IU). We were reassured by the manufacturers that no fault had been found with the rest of the supplied batch. Our patient was healthy apart from tuberculous lymphadenitis and had no history of any drug reaction or allergies. Her serum immunoglobulin concentrations were normal. The delay in the type IV hypersensitivity reaction, occurring on the fourth day after the Mantoux test, may be partly attributed to the hydrocortisone infusion.<sup>5</sup> The abnormal results obtained in the liver and renal function tests reflected the patient's hypovolaemic state secondary to the anaphylactoid shock.

As the tuberculin test will remain the most simple and important part of our antituberculosis programme in the community all doctors should be aware of its potential hazards, which may require immediate medical attention.

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## Natural killer cells in insulin dependent diabetes mellitus

Patients with diabetes mellitus have long been known to be predisposed to certain infections.<sup>1</sup> Less well known is the higher incidence of certain tumours—particularly pancreatic and endometrial tumours—in diabetes.<sup>2</sup> The aetiology of these infective and neoplastic lesions is likely to be multifactorial, although much recent attention has focused on the estimation of peripheral blood lymphocyte subpopulations.<sup>3</sup> These reports, however, have produced conflicting results. None of them mention natural killer cells, which are responsible for non-specific cytotoxicity and are said to represent the body's first line of defence as they attack cells with altered surface membranes such as virus infected and tumour cells.<sup>4</sup> To respond in this way these cells do not need to be primed by any other mechanism.

We, therefore, investigated the proportions and absolute numbers of

natural killer cells in healthy, insulin dependent diabetics with no known infection or neoplasia.

## Patients, methods, and results

We randomly selected 18 insulin dependent diabetics (10 men, eight women) for the study. All had been taking one of the highly purified forms of insulin for more than one year (median time taking insulin 4.5 years, range 2-10) and none had evidence of infection or neoplasia. Natural killer cell proportions and numbers were measured in these and in 48 age and sex matched healthy volunteers.

Peripheral blood lymphocytes from 10 ml of heparinised blood were isolated by density centrifugation on Ficoll-Hypaque and cell suspensions were incubated on ice with 2.5 µl of the various monoclonal antibodies used. These were anti-Leu 11 for natural killer cells,<sup>5</sup> anti-Leu 4 for T cells, anti-Leu 3 and 2 respectively for T helper and suppressor subpopulations, and finally anti-Leu 12 for B cells (all antibodies Becton Dickinson, USA). Analysis of cell populations was performed on a fluorescence activated cell sorter (FACS 420 Becton Dickinson, USA). In each case 5000 cells were analysed for fluorescence within the population criteria corresponding to lymphocytes defined by forward and right angle scatter produced by the cells as they interrupt the laser beam of the machine. By imposing limits of size and granularity that are proportional to this forward and right angle scatter not only can we concentrate on the cell population we are interested in but we can also exclude red cells, monocytes, and granulocytes.

The table shows that there were no significant differences between the diabetic and control groups for total number of lymphocytes (as assessed in a Coulter counter) or between the proportions of T cells, T helper or suppressor cells, or B cells. There was, however, a significantly lower proportion ( $p<0.005$ ) and absolute number ( $p<0.001$ ) of natural killer cells in diabetics.

### Lymphocyte subpopulations in diabetics and healthy volunteers (mean SD)

Lymphocytes	Healthy volunteers (n=48)	Diabetics (n=18)
Lymphocyte count ( $\times 10^9/l$ )	2.0 (0.8)	1.89 (0.75) NS
B cells (%)	6.4 (1.4)	4.51 (2.7) NS
T cells (%)	77.9 (3.5)	84.13 (5.33) NS
T helper (%)	53.6 (5.4)	56.95 (11.05) NS
T suppressor (%)	27.9 (4.1)	30.55 (12.05) NS
Natural killer cells (%)	16.0 (4.9)	11.21 (3.69) $p<0.005$
Natural killer cells ( $\times 10^9/l$ )	0.3 (0.1)	0.21 (0.09) $p<0.001$

Statistics by Student's *t* test. Natural killer cell number was calculated from the product of percentage natural killer cells and the total lymphocyte count.

## Comment

This study has shown that insulin dependent diabetics have a significantly lower proportion and absolute number of cells bearing the Leu 11 surface marker (interpreted as being natural killer cells) circulating in their peripheral blood than a group of healthy volunteers studied under the same conditions. We suggest that this may be a contributory factor when considering the causes of the known increased incidence of certain infections and tumours in these patients. The explanation of this phenomenon, however, remains unclear, and we do not know, for example, whether it is a result of the insulin used or a cause or effect of the underlying disease. Despite the obvious problems with controlling a number of variables in such a study, we believe that the phenomenon that we have described is worthy of more detailed analysis.

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